U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

U.S. FOOD AND DRUG ADMINISTRATION
AND NATIONAL TRANSPORTATION SAFETY BOARD
JOINT PUBLIC MEETING

TRANSPORTATION SAFETY AND POTENTIALLY SEDATING OR IMPAIRING MEDICATIONS

National Transportation Safety Board Headquarters
429 L'Enfant Plaza
Washington, D.C.

Wednesday, November 14, 2001
8:00 a.m.

BERNARD A. SCHWETZ, D.V.M., Ph.D.
Acting Principal Deputy Commissioner
Food and Drug Administration

CAROL CARMODY
Vice Chairman
National Transportation Safety Board

Chairmen

STEVE GALSON, M.D., M.P.H.
Deputy Director
Center for Drug Evaluation and Research
Food and Drug Administration

DR. VERNON ELLINGSTAD
Director
Office of Research and Engineering
National Transportation Safety Board

Technical Panels

Food and Drug Administration

DR. ROBERT TEMPLE, Director
Office of Medical Policy and
Office of Drug Evaluation I

Food and Drug Administration

DR. CHARLES GANLEY, Director
Division of Over-the-Counter Drug Products

DR. THOMAS LAUGHREN
Supervisory Medical Officer
Division of Neuropharmacological Drug Products

DR. ROBERT MEYER, Director
Division of Pulmonary and Allergy Drug Products

DR. RUSSELL KATZ, Director
Division of Neuropharmacological Drug Products

DR. PAUL ANDREASON, Medical Officer
Division of Neuropharmacological Drug Products

National Transportation Safety Board

DR. MITCHELL GARBER, Medical Officer
Office of Research and Engineering

PETE KOTOWSKI, Motor Carrier Specialist
Office of Highway Safety

DR. MARGARET SWEENEY
Transportation Research Analyst
Safety Studies Division
Office of Research and Engineering

RAFAEL MARSHALL, Project Manager
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Witnesses

Measuring Impairment

JAMES F. O'HANLON, Ph.D.
Santa Barbara, California

GARY KAY, Ph.D.
Washington Neuropsychological Institute
Washington, D.C.

Measuring Impairment

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Senior Vice President and Director
Science and Technology
Consumer Healthcare Products Association
Washington, D.C.

DR. JOHN WEILER
University of Iowa
Iowa City, Iowa

DR. BERT SPILKER, M.D., Vice President
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Education

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Warning Labels

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Advocacy Group

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Advocacy Group

DAVID WILLIS, President
AAA Foundation for Traffic Safety
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NEAL THOMAS
American Trucking Association
Alexandria, Virginia

DR. TOM FAULKNER
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TODD SPENCER
Owner-Operator Independent Drivers Assc.
Grain Valley, Missouri

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NORM LITTLER
United Motorcoach Association
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Operator Union Group

KAREN HEAD
Legislative Council
Teamsters
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CAPTAIN RANDY POPIEL
Allied Pilots Association
Fort Worth, Texas

Government Group

ROBERT M. CLARKE
U.S. Department of Transportation Washington, D.C.

Professional Group

RICHARD GELULA
Executive Director
National Sleep Foundation
Washington, D.C.

DARREL DROBNICH
Senior Director of Government and Transportation Affairs
Washington, D.C.

Also Present

DR. FRED TILTON
Deputy Federal Air Surgeon
Federal Aviation Administration

NANCY LaMONICA
Office of the Secretary
Department of Transportation

A G E N D A

P R O C E E D I N G S

8:00 a.m.

Administrative Announcements

DR. ELLINGSTAD: Good morning.

I think we will begin. We have given people a little extra time to get here and our apologies for the confusion that led some people to the freight elevator and apparently a considerable wait.

Welcome to an unusual meeting that's a joint effort of the U.S. Food and Drug Administration and the National Transportation Safety Board on Transportation Safety and Potentially Sedating or Impairing Medications.

I'm Vern Ellingstad from the National Transportation Safety Board. With me is Dr. Steven Galson from the Food and Drug Administration, and we will try to facilitate the efforts here today and tomorrow.

Before we begin the substance of the meeting, there are a few procedural announcements that we need to make. In the event of an emergency, such as fire, the building alarm system will activate and a voice message will instruct persons to vacate the building. You should proceed to the nearest exit. There are

emergency exits up front to the left and to the right of the platform and also at the back of the room.

Also for your convenience, restrooms and telephones are located in the foyer on the left as you exit the room.

To provide an appropriate meeting environment, I'd request that you set your pagers and cell phones to alert you silently to avoid interrupting the meeting. If this is not possible, please turn your device off. If you must use a cell phone, please do it outside of the meeting room.

To begin the meeting, I'd like to introduce Dr. Galson, who will introduce our first greeting from the Food and Drug Administration.

Steve?

DR. GALSON: Thanks very much.

I'm really extremely pleased today to welcome all of you, and I want to start by introducing our Principal Deputy Commissioner for Food and Drug, Dr. Bernard Schwetz.

Dr. Schwetz was from 1999, in September, until January 2001, Acting Deputy Commissioner of Food and Drug, and he served as a senior advisor for Science from September 1999 till June 2000. He was Director of

FDA's National Center for Toxicological Research in Jefferson, Arkansas, from 1993 to 1999.

He's a Diplomat of the American Board of Toxicology and an Honorary Diplomat of the American Veterinary Epidemiological Society.

Dr. Schwetz was the Acting Director of the Environmental Toxicology Program at the National Institute for Environmental Health Sciences in Research Triangle Park before coming to FDA in 1993.

Dr. Schwetz is a Member of the National Academy of Science's Institute of Medicine. In addition to numerous other professional awards during his career, Dr. Schwetz received the U.S. Government's 1998 Meritorious Executive Presidential Rank Award.

It's truly a pleasure for me to welcome Dr. Schwetz here today to open up the meeting for the Food and Drug Administration.

Thanks, Vern.

Opening Remarks

DR. SCHWETZ: Thank you, Steven.

Good morning to all of you. First, I'd like to acknowledge the important role that the NTSB plays in our nation's transportation safety and particularly over the past few days with the heroic efforts you're

making to investigate the tragic plane crash in New York City on Monday.

As devastating as that accident was, your quick work to investigate the cause has helped to calm Americans' immediate fears. Although the precise cause of the crash is not yet known, it helps to know that it doesn't appear to be another terrorist activity. We certainly wish you every success in that on-going investigation.

From the FDA, we're happy to co-sponsor this first-ever FDA/NTSB Joint Public Meeting. I'm glad to see that our two organizations take this opportunity to work together, to look at the role of sedating or impairing medications in accidents and related injuries.

I'd like to thank Mary Ann Blakey, the recently-appointed Chairman of the National Transportation Safety Board, and Carol Carmody, the Vice Chairman, and Dr. Vernon Ellingstad and his staff at the NTSB for assisting FDA in putting this meeting together, and I would also thank Dr. Ellingstad and Dr. Steven Galson from the FDA for co-chairing the meeting today and tomorrow.

I'm pleased to see the level and range of

expertise that is assembled here today on our panels and as witnesses as we consider the issues in front of us. So, thank you all very much for being here.

The FDA is certainly very supportive of NTSB's efforts to improve the safety of our nation's transportation operators, and we look forward to being part of this effort. Our former FDA Commissioner, Dr. Jane Henney, indicated last year that we would take this issue very seriously, and we continue to have this as a high priority.

Today's workshop demonstrates our commitment to consider all perspectives, including those of the transportation industry, other government agencies, and the public. We will also work with the pharmaceutical industry when considering recommendations that relate to labeling changes.

Well, what are the issues that we hope to address in these two days?

First. How can we increase awareness of the public about the possible impairment caused by prescription and over-the-counter drug products?

Second. How can we identify those products that cause impairment?

Third. How can we help the public avoid

taking products that will cause impairment while they're driving?

And fourth. Would relabeling those prescription and over-the-counter products help the issue?

By looking at the data available today, we hope to define the magnitude of the public health issue, both for transportation operators and for those with whom they share the roads, rails, skies and the waterways.

We'd like to look at possible mechanisms to screen for effects of time on driving, perhaps by looking at well-established assessment methods to see if they could be used to evaluate operators taking potentially problematic medications.

We want to identify the best ways to communicate the potential risks to the public. If we decide that labeling modifications are one effective way to accomplish this, what changes should be made so that labeling will be more informative to the user?

In closing, let me say that to the extent that drugs we approve are contributing to errors made by vehicle operators, we are very concerned. I assure you that we will take seriously any comments related to

this issue, whether the comments come out of this meeting today and tomorrow or whether they are submitted to the docket.

The issues are complex, but they're not insurmountable. So, we want to work together to help find solutions.

Thanks to all of you for participating in this meeting and for contributing your time, expertise and creativity. I'm looking forward to a productive session.

Thank you.

DR. ELLINGSTAD: Thank you, Dr. Schwetz.

I'm pleased now to introduce our Vice Chairman, Ms. Carol Carmody. Ms. Carmody worked for the Federal Aviation Administration from 1977 to 1988, including a tour as Deputy Director of Congressional Services. From 1988 to '94, she was an Aviation Staff Member of the Senate Commerce Committee. From 1994 to 1999, she was the U.S. Representative to the Council of the International Civil Aviation Organization, ICAO, in Montreal.

She was sworn in as the 30th Member of the National Transportation Safety Board in June of 2000 and appointed Vice Chairman on January 19th of 2001.

She served a stint this year as Acting Chairman, and she brings a considerable amount of experience to the transportation area.

Carol?

Opening Remarks

MS. CARMODY: Thank you, Vern.

Good morning. I'm Carol Carmody, as Vern said. Mary Ann Blakey was very sorry not to be here this morning. She had looked forward to this. I spoke with her yesterday evening, and, of course, she's occupied in New York but wanted me to send her regards and her wishes for a successful conference.

Before I get started this morning, I wanted to recognize the contributions of a couple of former government servants. Former NTSB Chairman Jim Hall and former FDA Commissioner Dr. Jane Henney. Those two really initiated this concept some time ago, and they deserve credit. I don't know if either is here today, but I did want to mention their names.

Also, the planning has been ably executed by Dr. Vern Ellingstad of our staff and by Dr. Steve Galson of the FDA, who are co-chairs of this conference.

I also appreciate the attendance and the

remarks very much of Dr. Schwetz. I appreciate what you said about the NTSB and about our efforts. We all feel that way, too.

Those of us gathered here today come from different sectors of society, from different agencies, and in some cases from different countries, but we all have the same goal, and that's to ensure safe travel for our citizens. Just as in the past, when faced with a problem, we have come together to work towards a unified solution.

Today, we're looking at an issue that we've known about for years: the fact that over-the-counter medicines and prescription drugs contribute to transportation accidents. We've made some recommendations to address certain aspects of this issue. Even so, we've not yet solved it, and it's clear that we need to learn a lot more.

Many medicines have long been known to cause drowsiness. Others may impair an individual's ability to fly an airplane, drive a car, steer a ship or operate a train. In fact, recent studies have shown that several over-the-counter medicines and prescription drugs can adversely affect an individual's performance without him or her being aware of it.

Since 1987, the NTSB has investigated over a 150 accidents in all modes of transportation in which over-the-counter medicines or prescription drugs caused or contributed to the accident. In aviation alone, over-the-counter medicines and prescription drugs played a part in 72 fatal accidents between 1987 and 1995. Since 1995, the numbers have been on the rise.

We at the Safety Board believe that the numbers may be even higher than we realize. Only a small percentage of people are ever tested for such drugs following an accident. So, we believe that they may contribute to more accidents than we're aware of.

So, we're faced with a tough question. How do we reduce the number of accidents caused by such medications when the extent of the problem is unknown? The answer is not simple. We must work together to expand testing programs to educate the public.

Last year, the Board made a number of recommendations, including expanding current toxicological testing requirements to get appropriate samples from fatal transportation accidents, so we could determine what effect these prescriptions and over-the-counter medicines are having.

The Board proposes expanding educational

programs and providing better warning labels on the medicines.

All of us here today understand that when education can prevent accidents, it's our responsibility to provide that education to the public. To all of the people operating planes, trains, cars, buses and ships, they deserve to know what effect drugs will have on their performance.

We should also recognize the efforts to date, and there have been many. The Department of Transportation and its many modal administrations as well as many other organizations here today have taken steps to reduce the number of accidents caused by over-the-counter medicines and prescription drugs.

The NTSB commends these efforts. As always, we want more. We recognize that more needs to be done, and we must do it together. Certainly none of us would be here today if we didn't think there was more room for work.

Both the NTSB and the FDA appreciate the attendance of everyone today, the experts, the participants, and those of you in the audience, and I think we're one step closer to a common solution.

Thank you.

DR. ELLINGSTAD: Thank you, Vice Chairman Carmody.

Before we begin, we'll kind of outline the sort of procedures that we will follow today and tomorrow in this public meeting. I'd like to sort of make it as clear as we can what this meeting is and is not.

It is not an adversarial proceedings. It is not a hearing. It is a public meeting designed to elicit information and to provide information that will inform both the FDA and the NTSB with respect to our interests in this particular topic.

The way that the meeting will proceed is through a series of witness panels. The panels, the members of the panels will each make a short presentation and then respond to questions. The questions will be directed by a technical panel composed of staff members from the FDA and the NTSB, and questions will also be solicited from a number of -- those who are familiar with NTSB proceedings, referred to as parties, and we will in a moment introduce who these parties are.

But each of the party groups representing various constituencies affected by the issues of drugs

in transportation safety will have an opportunity to pose questions to the witnesses.

When we have completed that round, and we will try to do that as equitably and fairly as we can, we will pass the questioning back to the Technical Panel. Dr. Galson and I reserve the right to butt in and ask questions, if we desire.

We will also solicit from the audience questions in writing that will be forwarded up here to the podium and whichever of us is not moderating a particular panel will sort those out, and we will pose those questions also to the panel.

Time is of something of an essence, and we will try to maintain a schedule better than our starting time was maintained this morning. So, we would appreciate that all of the presentations as well as the questions be kept concise.

The staff will circulate among the audience and hand out cards that will contain the questions that will be brought up here. So, if you see staff with cards, if you have a question, draw their attention to that and send them up.

Another thing that is a little bit unusual in terms of proceedings that the Board has been involved

in is the provision for audience presentations, and there will be two of those. One this morning at approximately 11:15.

Anyone desiring to make a short five-minute presentation should contact the desk in the lobby area, and we will only recognize individuals who have registered to do that, and they will be called on to make those short presentations today at 11:15, and there's also another session that's set aside for that tomorrow.

What I'd like to do, I believe that Dr. Galson has a couple of administrative announcements with respect to the opening of a docket of this meeting, and then I'll ask him to also introduce the FDA members of the Technical Panel. When he's done with that, I'll catch the NTSB members of the panel.

Introductions

DR. GALSON: Great. Thanks.

FDA, in our regulatory capacity, is required to have a copy of all of the presentations in writing and filed to the FDA docket, and the docket number for this meeting is 01N0397. Please make sure you file the copy of your presentation, and if you've not, give a copy to the FDA representatives out at the table.

Also, any special requests for copies of the presentation from this meeting should be asked for at the Registration Table if people in the audience want copies, and they'll be mailed to you at a later date.

We'll put a transcript of the meeting on our FDA website by the middle of December.

I'd like to quickly introduce our Technical Panel that are here from the agency. We've really got an all-star cast of experts sitting up at the table over here, and folks, if you'd just raise your hand, so folks know who you are.

Leading the team is Dr. Robert Temple, who's the Director of two offices in the Drug Center, the Office of Medical Policy and the Office of Drug Evaluation I.

Dr. Robert Meyer is the Director of Pulmonary and Allergy Drug Products. Charlie Ganley is the Director of our Over-the-Counter Drug Products Division. Russell Katz is the Director of our Division of Neuropharmacological Drug Products. Tom Laughren is the Supervisory Medical Officer in the same division, and Paul Andreason is a Medical Officer in the division as well.

So, thank you, FDA experts, for being here,

and we look forward to your active participation.

DR. ELLINGSTAD: I'd like to introduce the NTSB's staff who are serving on the Tech Panel and will make themselves known with questions throughout the course of today and tomorrow.

First, Dr. Mitch Garber is the Board Medical Officer, and I'd like to give a special acknowledgement for his very extensive effort in coordinating this whole activity.

Next, Mr. Pete Kotowski, a Motor Carrier Specialist and Accident Investigator with the Board's Office of Highway Safety. Dr. Rafael Marshall, Project Manager and Investigator, also in the Office of Highway Safety, at the NTSB, and Dr. Meg Sweeney, the Transportation Research Analyst in our Safety Studies Division, here at the Safety Board.

I'd like also to acknowledge the participation of the various parties, and what I'd like to do very quickly is go around, and we'll do this in an orderly sort of way to begin with at least, and I'll ask -- we'll go to each of the tables and ask each participant at the various tables to introduce themselves.

I'd like to also mention that in the interest

of expediency, what we will ask each of the tables to do is to designate a spokesperson for the purpose of questioning of our witness panels. We aren't going to have an opportunity to go and have everybody at every table ask questions, but if you will provide designated spokesman -- provide your questions to that spokesman, and we can handle the questioning in that particular way. We certainly can rotate that spokesman duty during the course of the two days.

Okay. Let me start over on my right with the Union table. Push the button.

CAPTAIN POPIEL: Randy Popiel, Allied Pilots Association.

DR. ELLINGSTAD: Thank you.

And the Industry Table. Try it again.

MS. TAUBIN: Lorna Taubin, representing the Consumer Healthcare Products Association.

DR. ELLINGSTAD: Okay. And we have another Industry Table, a Transportation Industry Table.

CAPTAIN DeLEONARDIS: Captain John DeLeonardis, representing the Liberian International Ship and Corporate Registry.

MR. SPENCER: Todd Spencer with the Owner Operator Independent Drivers Association.

Operator Independent Drivers Association.

MR. LITTLER: Norm Littler with the United Motorcoach Association.

MR. MAHORNEY: Bill Mahorney with the American Bus Association.

MR. THOMAS: Neal Thomas with the American Trucking Association.

DR. FAULKNER: Tom Faulkner with the Air Transport Association.

DR. ELLINGSTAD: Thank you.

And the Advocacy Group Table.

MS. TARNEY: Karen Tarney, Citizens Against Drug Impaired Drivers.

MS. CHRISTOPHERSEN: Asbjorg Christophersen from the National Institute of Forensic Toxicology in Norway.

DR. de GIER: Johann de Gier, International Council on Alcohol, Drugs and Traffic Safety.

MS. SANDER: Nancy Sander, Allergy and Asthma Network, Mothers of Asthmatics.

MR. WILLIS: David Willis, AAA Foundation for Traffic Safety.

DR. ELLINGSTAD: Okay. And the Government Table? Why don't we start -- go ahead.

MR. CLARKE: Bob Clarke, U.S. Department of Transportation, Office of the Secretary.

MS. LAMONICA: Nancy Lamonica, Department of Transportation, Office of the Secretary.

MS. STEVENS: Judy Stevens, Centers for Disease Control and Prevention.

DR. ELLINGSTAD: Okay. Thank you.

Okay. Without further ado, we'll go to the Witness Panel, the first Witness Panel dealing with the topic of Measuring Impairment, and what we will do with this panel is kind of go right down from my right to left.

Let me just very quickly introduce and kind of give the rules of engagement for this group. We'll ask you each to confine your set of opening remarks to five minutes, and we'll trust the Technical Panel and the parties to elicit the additional information that you have brought along.

We'll start with Dr. John Weiler from the University of Iowa.

Witness Panel I - Measuring Impairment

DR. WEILER: Are we ready with the slides?

Thank you for the opportunity to be here and talk about the use of driving simulators to measure

impairment in driving.

Next slide. There are a variety of medications that may impair performance, and I've listed some of them on this slide, including anabolic steroids, anesthetic agents, anti-anxiety drugs, anti-depressants, caffeine and stimulants, and the remainder of the drugs, one that's very concerning to us and to me as an allergist would be those drugs we use to treat respiratory disease.

We also are concerned about drugs given to the elderly and combinations of drugs and, of course, drugs that may be abused.

Next slide. Now, sedation is the issue, but sedation can be broken into drowsiness and impairment. It's easy to measure drowsiness. It's a subjective feeling, and we record the numbers. It's much more difficult to measure performance impairment, and that is an interference with the ability to perform a task or tasks measured objectively.

If the patient experiences drowsiness only, that's a subjective feeling that's not pleasant, but performance impairment only is a very serious problem because the patient doesn't have the idea that the person is impaired. If the person has both, then

hopefully the drowsiness will be a cue not to do the task.

Next slide. We can ask a variety of sample experimental questions, and these are some of the ones that we've asked, such as do first-generation sedating antihistamines cause performance impairment as compared with non-sedating antihistamines, when measured, using a high-fidelity driving simulator, and if yes, can the subjects predict impairment based upon drowsiness or upon their feeling of being impaired?

Next slide. What I would like to show you is a very small video clip of the new National Advanced Driving Simulator that will allow us to do some studies that were not possible before this facility was completed. Let's put the video in.

(Videotape shown)

DR. WEILER: We'll just keep going on with the slides, and hopefully we can come back to that at some time later.

Next slide. Next slide. Unfortunately, that shows you the ability to do some of the tasks that are described on this slide as end points. The fidelity with that simulator will be something that will be unmatched in the future, the ability to look at all of

these many end points, including lane tracking, lane excursion. Obviously, it's very important that we keep within our lanes. Steering instability, ability to follow a car. We can measure a variety of end points for that. Curve trajectory, staying within the lane, speed control measures.

Eye tracking is a very important and a very interesting end point that we're looking at with a variety of different new pieces of equipment. The percent of closure of eyes and things that would tell us that someone is impaired and is about to nod off. Head tracking.

Next slide. We can look at responses to events, subtle events, repeated events, and events that are potentially life-threatening, and we can do that in a simulator that we couldn't do on on-the-road driving.

We look at subjective drowsiness, and we correlate that with objective measures, and we correlate subjective feelings of being impaired with subjective drowsiness. Then we look on the other side of subjective feeling of being impaired, and does it correlate with objective measures, and does it correlate with drowsiness?

Next slide. There are a lot of advantages of

the use of the National Advanced Driving Simulator and perhaps we can show you actually a picture of it later. We can use realistic crash scenarios, put people in harm's way that we couldn't in on-the-road driving. The tasks are realistic. We can control traffic both in lane and in the oncoming lane and with high-density traffic with people who are impaired. We can look at a variety of weather conditions.

We have a high-fidelity image generator that is a 20/20 image in the center, something that has never been possible before. High-fidelity motion, so the motion is what you would feel in on-the-road driving, and we have tremendous flexibility in designing the scenarios, both rapidly, and they're very realistic, and finally is the fully immersive environment.

Next slide. So, in conclusion, driving simulator studies have been accepted as demonstrating performance impairment. They may be more expensive than other kinds of studies, but the rewards may justify the cost if lives are saved.

The National Advanced Driving Simulator will indeed be a unique facility to study human performance in a variety of settings that have not been possible in

the past. It will offer us an opportunity to cross-validate lower-fidelity simulators and other tests.

The bottom line is that driving is a real world task. It's very important to many of us.

DR. ELLINGSTAD: Thank you, Dr. Weiler.

Our next panelist is Dr. James O'Hanlon from Santa Barbara, California.

DR. O'HANLON: Good morning.

Can you hear me? Fine. I have two points to make today; that is, that we have the technology for screening drugs in the registration process. We've had it for nearly 20 years, and this procedure will lead to a labeling system, an example of which that I will show today.

May I have the first -- actually, the second slide. That just says who's talking.

We, beginning in 1981, began developing an over-the-road driving test for assessing the effects of medicinal and recreational drugs. We standardized that test two years later, in 1984, and essentially it has been applied in more than 45 major studies, unchanged ever since.

We've used it with psychiatric patients, depressed and anxious. We've used it with cognitively

impaired elderly and mostly with healthy volunteers. The test is recognized by the EMEA, which is the FDA's equivalent in Europe, as valid for assessing the effects of certain drugs, specifically hypnotics and anxiolytics.

May I have the next one, please? I haven't brought pictures of this test because we've done everything we can to make it appear completely naturalistic, both to the subjects of the test and also to the other people in the driving environment with whom they interact.

The safety is supervised in this test by an on-board licensed driving instructor. The test begins with the test subject or patient entering a primary highway into normal traffic and proceeding 50 kilometers, 30 miles, in one direction, exiting and returning and returning 50 kilometers to the origin.

During this time, speed and lateral position of the vehicle are measured by automatic means. The standard deviation of lateral position measured over the entire test is the primary outcome variable. It is a measure of -- combined measure of swerving and weaving, and we call that SDLP from now on.

I'm using one example of the work that we did

together in the Netherlands until my leaving in '98. I must add that it continues today under other direction.

The example I've chosen is an example of hypnotic drugs. We have studied nearly every hypnotic drug available in Europe and the United States, and the way we do it is administer the drug to the patient or the volunteer and allow them to sleep. We test -- we have tested patients and volunteers five to 17 hours after drug ingestion.

The experiments. There have been about a dozen in number. They have all followed double-blind placebo and active control designs in a number of different experiments, with an exceptional case of 12, usually 18 to 24. The power for detecting a significant effect of the drug has always been better than 90 percent.

May I have the next one, please? The next one. Now, the reason that we're interested in the residual effects of hypnotic drugs is because we have a little epidemiological information to indicate that that problem is most severe.

Flurazepam or Dalmane, as it's called in the United States, was the first benzodiazepine registered in this country. It has been shown in epidemiological

research to increase the risk of an injurious accident more than five times normal, which is the equivalent to driving with a blood alcohol concentration of .95 milligram per milliliter or in the United States term, .09 gram per deciliter.

So, I'm going to be talking in the European units, but if you'd like, just put a zero in front of that 9, and you will have the units here.

In the old dose, Triazolam or Halcion raised the relative risk of injurious accidents more than three times. There is a drug available in Europe but not here. It's supposed to be a slow-acting drug and very safe, according to the manufacturer, but it was shown in England to raise their risk of injurious accident four times, which is the equivalent of a blood alcohol concentration of 0.8.

Next slide, please. I have too much data to discuss in detail. I would just like you to concentrate on the three bars to the right. This is average standard deviation of lateral position SDLP over a one-hour ride, 10 hours in the blue bar after taking the drug, and the red bar, 16 to 17 hours.

These all are hypnotics with very long half life, but I would like to focus on Flurazepam, a drug I

already mentioned, Dalmane. We have studied it three times, twice with patients, once with volunteers, and we have measured a greater effect of that drug 10 hours after administration than produced by a blood alcohol concentration of .10 or drunk in every one of the American states. Even 16 to 17 hours after administration, the effect is still greater than a blood alcohol concentration of .05.

I would like to go quickly over the next slide, just actually look at -- glance at it briefly. These are intermediate-acting hypnotics. They have less effect. These are not in the system so long but still, as you see, some of them are impairing the next morning and even in the next afternoon after ingestion.

The next slide, please. Modern hypnotics are very short-acting. The two that are quite popular in the United States, one is Zaleplon or Sonata is the trade name. The other is Zolpidem, ZPD up there, and it is called Ambien in the stores.

When you look at either one of those drugs, the first three bars on the left, 10 hours after ingestion, neither one of them has an effect, and even Zaleplon in 20 milligram dose, which is twice recommended, still has no effect. But how close to the

time of awakening can you take it?

I skip over the nasal amitrazalem bars, and going now to where it says in the top, "Five to six hours after administration", we've measured the effect of Zaleplon here and of both 10 and 20 milligram doses. Again, they're not significant. We'll leave the Zoplicone bar. That's a European drug.

Now, far over on the right, here is taking the drug only four hours before the test, and here, you see Zaleplon 10 and 20 milligram have no effect. Zolpidem 10 milligram, the registered dose, has an effect greater than .05 blood alcohol concentration, almost .08, and if you would take twice the dose four hours, you could see that the effect is greater than .10 blood alcohol concentration.

Last slide. From these data, we are able to make pictograms which precisely and informatively allow the user to know what to expect from a hypnotic drug. These are only two categories. We've actually published a six-category system, and it could even be expanded, but in this, for the two examples I've just given of Zaleplon and Zolpidem, we don't know how long it would be dangerous to drive after Zaleplon. We only know that after four hours, it had no effect.

So, we say zero to four hours, you are forbidden to drive, according to our recommendation. After that, you are free to drive for the next 24 hours. With Zolpidem, a very good drug, a very safe drug, still again we haven't tested it before four hours, but we advise people not to drive. We have tested it four to five hours. There was an effect, and so we say all right, from that point until the next time we've tested it and found no effect, you drive with great caution because the effect we anticipate is greater than the blood alcohol concentration of .05, and after that, you're free.

We have done this for many drugs. The worst of them, Dalmane, as I showed you, has red around the clock. You should never drive using that hypnotic in 30 milligram doses. We think this is a reasonable way of portraying crucial information to the patients who use this drug.

Thank you.

DR. ELLINGSTAD: Thank you, Dr. O'Hanlon.

Our next panelist is Dr. Gary Kay from the Washington Neuropsychological Institute in Washington, D.C.

Dr. Kay?

DR. KAY: Good morning, and I appreciate the opportunity to speak to you.

If we can go to the first slide, my comments will be more general on how we measure impairment, what the methodology is and extent to which we have advances in this methodology currently.

I think one of the reasons why we're here, if you'll show the slide, why we're here is that the public has little awareness of the risks associated with taking especially sedating over-the-counter medications, and often, there is a belief that if you don't feel drowsy, that in fact you aren't sedated.

But as Dr. Weiler has shown, go on to the next slide, next slide after that, please, in fact, a depressant medication's effects on the central nervous system could be manifested different ways. In fact, you may feel sleepy. You may feel drowsy. That's your personal experience. Often, people have -- they think the definition of sedation is drowsiness, but it's more.

In fact, there could be changes physiologically in brain activity. There may be a change in your ability to stay awake during the day. There may be a detrimental effect on your performance.

In fact, if we are going to evaluate medications and give an honest appraisal about whether a medication is sedating, we must use all of these methods. We must find out do people feel drowsy or sleepy? Are there physiological changes? Are there performance changes?

With respect to self-report measures, commonly we use diary cards. Often, there's too much reliance on diary cards. There are rating scales, visual analog scales. There are newer devices, such as the use of personal data systems, like Palm Pilots, and there's also data we can obtain from prescription event monitoring.

Taking a look at the new methodology of the use of these personal data systems, these provide us with very high subject compliance. You actually program them to inquire of the subject at different points during the day about their current subjective level of sleepiness. You get a time logging of these entries, and there's improved data handling. They were recently demonstrated at the DIA Conference in Denver to be superior to the paper diary.

The problem with self-report measures are that they are subjective. There may be biased reporting. There is poor diary compliance, and as Dr.

Weiler pointed out, there's low agreement often with physiological and performance measures.

Somebody may report no self-reported sleepiness, but in fact show physiological impairment or cognitive impairment or in fact driving impairment in the absence of any self-reported sleepiness. We do have physiological measures. I've listed some of them here for you. EEG.

At Georgetown, we've been working with functional brain imaging. Sleep latency testing has been around for awhile, and there's activity monitoring as well.

Here is some data from one of our studies at Georgetown where we are looking for the physiological and subjective. This is night-time, 10 p.m., dosing with Chlorpheniramine. The red is eight milligram, the purple 12 milligram Chlorpheniramine at 10:00.

Looking at the next day, from 9 a.m. till 5 p.m., the number of -- average number of minutes before people fell asleep during naps, and what you're seeing here is that for placebo, we have a normal sleep latency greater than 10 minutes, but for either the eight or 12 milligram Chlorpheniramine, taken 10:00 the night before, the next day, the sleep latencies drop

down to six minutes, both statistically significant but clinically meaningful as an evidence of excessive day-time somnolence, and looking to the right, it's indicating that on the Stanford Sleepiness Scale, the subjects who received the eight milligram dose of Chlorpheniramine are reporting no more sleepiness than the patient who received placebo. They had no awareness of their sleepiness.

This is looking at the results from our functional brain imaging. We're looking at changes in brain activation with -- while people are performing a mental arithmetic test after they've been dosed with again eight and then 12 milligram Chlorpheniramine. The white is placebo. This is showing you the brain imaging. The left side shows what activates during training. The right side under retesting with placebo, there's only one-quarter the amount of activation once you've learned to perform an activity in the FMRI.

If you know you're looking at another subject here on the left side that's training, the right side, this is three days of dosing Chlorpheniramine at night, looking at day-time performance in the FMRI, and you're seeing actually five and a half to six times an increase in the amount of brain activation.

Now, those are physiological. Lastly, we have performance measurements, and performance measurements include tests of thinking or cognition, tests of skilled motor activity, psychomotor, and as you've heard from the first two speakers/witnesses, simulation testing.

In terms of what we're doing currently to measure cognitive functioning, we are using a lot of computer-based neuropsychological tests, and these are tests that we initially developed largely to look at early-on chemical defense and did a lot of this work in the Department of Defense.

These methods provide us a number of advantages. There is standardized instructions, standardized presentation of stimuli. There's enhanced sensitivity over traditional paper and pencil-type testing, highly accurate measures of speed and accuracy. They can be designed using computer-based testing methodology with a lot of different sponsorship. Department of Defense, Food and Drug Administration, and pharmaceutical industry.

This is showing you basically a screen of somebody taking the cog screen test. They are not going to use a keyboard. We basically keep them up on

the screen using a light pen. You may test a whole room full of people all at one time. This is a test item for you to practice, memorize that, which one's the same, left or right. Hopefully you choose right.

This would be a divided attention test that involves working memory at the top. Remember the previous number being shown in that top square, and then a tracking test where you maintain that blue square in the center of the screen. You do both of these tasks at once. It's a very good predictor, sensitive to changes and shift and that kind of thing.

The test which we find most sensitive to sedating impairing drugs are tests of vigilance, the ability to sustain attention during a boring activity. Divided attention. Your ability to perform simultaneous mental activities, like perform the tracking at the same time that you're doing some other type activity. Working memory, holding information temporarily in your mind.

This is just showing you a very simple 12-minute test. We've actually recorded this on to a Palm Pilot, and looking here at Diphenhydramine in yellow, 50 milligrams, versus placebo, basically you're looking at four times the number of lapses of attention for a

subject taking a common over-the-counter sedating antihistamine.

This is a study we just did, sponsored by FDA, actually looking at very low dose over-the-counter antihistamine, Chlorpheniramine at two milligrams and four milligrams versus placebo, and this is looking seven hours post-dosing. Nobody's reporting any sleepiness. Stanford Sleepiness Scale scores all below two, yet there is impairment on our dual task tracking test for the subjects at either dose in the absence of feeling sleepy.

Summarizing for you. Sedating medications can cause impairment in the absence of sleepiness. Sedating effects may carry over to the following day, even when the medications are taken the night before, and the functions which we believe are most vulnerable to sedating medications, which we've demonstrated, are in fact vigilance, very important in transportation safety.

Psychomotor skills under divided attention obviously involved in transportation and working memory. We have, we can provide reliable and valid measures. They are available. We're evaluating all of these dimensions of sedation, self-report,

physiological and performance.

Thank you very much.

DR. ELLINGSTAD: Thank you, Dr. Kay.

Our next panelist is Dr. Bert Spilker, Vice President of the Pharmaceutical Research and Manufacturers of America here in Washington, D.C.

Dr. Spilker?

DR. SPILKER: Good morning.

I'm Dr. Bert Spilker, Senior Vice President of Scientific Regulatory Affairs for the Pharmaceutical Research and Manufacturers of America.

PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. In regard to the subject of this panel's discussion, I wish to make seven points.

First. Every investigational drug is carefully and thoroughly evaluated for adverse reactions it may cause.

Second. These evaluations are conducted in both artificial as well as highly-controlled clinical trial settings during Phase I and II of development of a drug, and, in addition, in close to real world clinical settings during the Phase III development.

Three. Evaluations are made through adverse

drug reporting via spontaneously-volunteered verbal communication by patients in diaries recorded by patients when they're kept as part of a trial and in responses by patients to written questionnaires for quality-of-life and for other tests.

Responses to verbal non-biased questioning, such as, have you had any problems or noticed anything different since you were here last, are the basis for collecting adverse drug reactions during each phase of drug development.

Four. Any real world or real life events, such as traffic accidents during a clinical trial, is collected as an adverse event, no matter how mild, and every attempt is made to ascertain the cause, whether it be drug-related or non-drug-related; i.e., the accident could be due to drowsiness due to the drug or from an event due to the disease under evaluation or from other non-drug-related causes prior to the accident.

Five. Adverse drug reactions for an investigational drug are compared against placebo and often versus other approved drugs prescribed for the same disease, either in head-to-head clinical trials or using data from the respective package inserts.

A benefit-risk determination is eventually made by the sponsoring company and by the FDA, and drugs are allowed on the market if their benefits exceed their risks.

Six. After market approval, adverse drug events that a company learns about through its post-marketing surveillance program or global safety network, as described in the Code of Federal Regulations, are sent to FDA on an expedited or periodic basis. The company's network captures reported ADRs occurring anywhere in the world.

Seven. The relationship between drowsiness as an adverse drug reaction and impairment of performance has not always been demonstrated to be related or correlated. Drowsiness tends to be a subjective feeling, whereas impairment is based on more objective testing.

Various methodologies have been utilized to evaluate performance impairment in both real life and clinical trial situations when certain adverse drug reactions, such as drowsiness, have been associated with its use in some patients.

There are more than a dozen commonly-used tests that measure performance impairment. However,

there is no accepted universal standard approved by FDA for testing impairment in a clinical trial setting, and a validated reference for what may be a clinically meaningful threshold of impairment is not presently agreed.

In conclusion, well-documented methodologies are currently being utilized during the development phases of a drug for evaluating adverse drug reactions and their potential relationship to performance impairment.

Once a drug is approved for marketing, the drug's safety profile continues to be monitored through post-marketing surveillance programs with resultant relevant updating of prescribing information based on the additional information.

Thank you for the opportunity to address this group, and copies of my talk are available in the table outside.

DR. ELLINGSTAD: Thank you, Dr. Spilker.

Our final witness on this panel is Dr. William Soller, Vice President and Director of Science and Technology for the Consumer Healthcare Products Association.

Dr. Soller?

DR. SOLLER: Could I have the slide, please?

Thank you, Dr. Ellingstad, Dr. Galson. Good morning, and thank you for the opportunity to be here.

I'm Dr. Bill Soller with the Consumer Healthcare Products Association, a 120-year-old trade organization representing the manufacturers and distributors of non-prescription medicines and dietary supplements.

Do I ask you for the next slide? It didn't seem to be working. I think I'll do it orally, if I may.

My remarks focus on OTC antihistamines, a class of OTCs with a drowsiness side effect. OTC antihistamines are highly effective for treating symptoms of allergies, runny noses and sneezing associated with the common cold, for nausea, and for some ingredients as sleep aids.

OTC antihistamines have been thoroughly evaluated under the OTC review by FDA and its expert advisory panels, including a detailed examination of the chief side effect, drowsiness, the concern about driving and operating machinery, and the creation of special warnings for this side effect.

FDA and its panels concluded that there is a

wide range of susceptibility to the drowsiness effect with less than 10 percent to up to 50 percent of users experiencing drowsiness, depending on the antihistamine used, the dose and the underlying condition.

FDA and its panels also created specific carefully-worded drowsiness warnings for different classes of antihistamines, depending on the degree of drowsiness associated with their use. In so doing, they created in detail or they considered in detail the potential for machinery-related accidents and the potential exacerbating drug interactions.

With this warning and other labeling, OTC antihistamines have been determined to be generally recognized as safe and effective.

Next slide. Antihistamine containing OTC products bear a specific drowsiness warning shown here. Though drowsiness may occur, it does not always occur in all users. Alcohol and drug interactions are identified, and there's a specific caution about motor vehicle and machinery operation, and I might add, studies support the fact that consumers read the label before using the product the first time, and CHPA has had a very long involvement in educating consumers on the need to read and heed the OTC label.

Next slide. We conducted a 10-year post-marketing surveillance analysis for these OTC antihistamines in single and combination products, looking at AERs with an accident-related term in persons 16 years or older. The accident term was defined very broadly to include all forms of transportation accidents and other possible related terms, including falls, injured limbs, and so on.

Next slide. Over this 10-year period, there were a total of 23 serious AERs with antihistamines as a primary or suspect -- secondary suspect drug with an accident term in any field of the AER. There were no more than four AERs in any one year over this period.

About 850 million OTC units for adults alone were sold during this 10-year span, and I might add there are also RX uses for certain of the drugs studied. These findings were supported by previous studies by the National Highway Traffic Safety Administration, Ray et al., and Turnbridge.

In a study in the early '90s by the National Highway Traffic Safety Administration, post-mortem blood samples were analyzed from over 1,800 drivers in seven states. NHTSA concluded this and other studies have found that there are relatively few drugs which

have prevalence large enough to present a highway safety problem. These were mainly drugs of abuse.

Ray et al. determined the risks for injurious crashes for drivers who had received prescriptions for various drugs, including prescription and crash records, for over 16,000 elderly drivers in Tennessee. However, the relative risk for current users of only RX antihistamines was 1.2 with the confidence limits spanning one, and no dose effect was demonstrable.

We therefore in these long-term larger-scale epidemiologic studies see no signal for concern. We conclude that the OTC warning label and educational programs are having an impact.

May I have the next slide, please? With the new drug facts label, there will be even better communication with the consumer. On the left is the old label. On the right is the drug facts label. Note the more consumer-friendly format that allows a more prominent and more consistent placement of the drowsiness label across the product categories.

You may not be able to read it from the audience, but the warning appears when using this product, marked drowsiness may occur and so on, in the middle of the label.

May I have the next slide, please? In conclusion, OTC antihistamines have a demonstrated history of safe and effective use when used according to label directions. OTC antihistamines are appropriately and adequately labeled. Drug facts label will make the warning label even better.

CHPA believes that it's important to maintain an on-going program of consumer education on the importance of reading the entire OTC label.

Thank you.

DR. ELLINGSTAD: Thank you, Dr. Soller, and thank you to the panel.

What we'll do now is turn to our Technical Panel for a round of questioning. I'd again like to remind the people in the audience that if they have questions that they would like asked of this panel, please identify the staff that are roaming around and obtain from them a card, write your question down and hand it to them, and they'll bring it up here, and we will ask those questions.

I'd also like to remind the party groups to think about their questions and to identify their spokesperson here, and we will, after the Tech Panel is done with their questioning, begin a round of questions

from the parties.

To lead off the Technical Panel questions, Dr. Garber will start.

Questions from Technical Panel/Parties and Discussion

DR. GARBER: Thank you. Thank you very much, Dr. Ellingstad, and thank you very much to the panel. I really appreciate your presentations.

I do know that we had a little bit of audio-visual difficulty with Dr. Weiler's presentation with his videotape. Has the video tape problem been corrected? Can we show that video tape now? I just wanted to give Dr. Weiler an opportunity to present that, if in fact that's -- we have that ability now.

DR. WEILER: I believe we can certainly show it. I believe we can show it now. I guess it's coming from the booth as opposed to from down here.

(Video tape shown)

DR. WEILER: This is an animation of the National Advanced Driving Simulator, and it demonstrates the X, Y, and you can't see the Z access. You'll see that when we zoom in on it.

But it's a facility that exists in the Oakdale Campus at the University of Iowa, and here we see zooming in on the facility itself. This is the

control room that runs the facility. You can see off in the bay the dome structure that contains the cab. We have currently four cabs that we can use in that dome structure, two sedans, a tractor-trailer front end and an SUV.

This is all animation demonstrating driving maneuvers. There's 360 degree of visuals, something very unique. Here, we see the actuators, and this is what gives us the feeling of motion. It's very realistic. So, we can set crash scenarios that really wouldn't be possible with on-the-road driving.

This is a demonstration of a spin-out. This is what the subject would actually see while driving the car. Both the sound and the feel are very realistic, and we can record all of the end points that I showed on the slide. It can help us to understand what happens.

We have in-town driving. We can pick tiles to set these up very rapidly, so that you can have a scenario that's in town and quickly goes to a rural setting. We can repeat these drives with every individual. We have triggers on the roads, so that when you drive over a trigger, it may cause something to happen, such as somebody jumping out in front of the

car.

It's extremely easy to set this up, and we have data reduction tools that allow us to collect the data and analyze them quite rapidly. It is an $80 million facility, so it's not something that we can do for every drug and every test, but it does allow us some tremendous flexibility in being able to run studies in ways that really weren't possible in the past.

Thank you.

DR. GARBER: Thank you very much.

I just have actually just one question, a quick question, for the entire panel, and I'd like to get an answer from each of the participants, if I may, so that we can quickly get this to the parties after our FDA counterparts have also asked their questions.

But the only question I have, and this is for each of the members, is, do we have the capability now, given the tests and the data that we have available, do we have the capacity to identify drugs which we do know do not impair vehicle operators?

In other words, can we reliably identify or compile a list of drugs which we now know or which we can readily identify fairly shortly that do not in fact

impair vehicle operators that we can declare relatively safe for their use?

I'd like to pose that to each of the panelists.

DR. WEILER: There probably are a group of drugs that have been studied to some extent. The problem is that I believe that the drugs that don't cause drowsiness to any great measure probably haven't been studied very well for their impairing capacity.

So, if we believe, as we've shown with the antihistamine classes and with other drugs, that drowsiness and the subjective feelings don't predict impairment, the problem is the drugs that are either mildly or not very sedating at all have really not been studied in any great way for impairment.

So, we can make guesses, but I'm not sure that it would be entirely accepted by everyone.

DR. O'HANLON: I disagree with my colleague. I think we know a number of drugs which are not impairing, relatively, of course. There can always be an impaired -- one impaired person out of a thousand or whatever, but in the -- for the drugs that I would call non-impairing, they have no significant effect at the recommended dose, no significant effect at twice the

recommended dose and sometimes higher, up to four times, and there is no individual in a representative group of, say, 24 to 32 who shows an anomalous untoward reaction.

Now, having said that, the caveat I have to add is that in our tests in the Netherlands, we did not study every population of drivers, and what I'm saying now pertains to young either patients or volunteers and not elderly patients or otherwise impaired drivers.

So, with those caveats, yes, we have a number of drugs in every therapeutic class, that we have nearly every one that we've defined as safe.

DR. KAY: The only thing I would add would be that if we used as a criteria lack of evidence of sedation meaning no findings on self-reported sleepiness, no findings of problems or abnormalities on physiological tests of sedation or performance measures, we have very few drugs we've tested across all those, you know, types of measurement.

That was in fact a lot of the work being done in the Department of Defense when we were doing work on chemical defense drugs and looking to find out which drugs you could take and still fly a plane, which drugs you could take and still drive a tank, and we did study

certain medications but very few have been studied across all of those domains and dimensions of testing.

DR. SPILKER: It's well known that people react quite differently to any drug, and it's difficult, if not impossible, to say that Drug X never causes drowsiness.

If you look in the PDR, you will see that many, many drugs not associated with sedation and impairment certainly also have drowsiness listed as an adverse reaction.

So, I think it would be a disservice to say to any group these are drugs that do not cause drowsiness or sedation. I think we'd be sending the wrong signal medically.

DR. GARBER: Just as a follow-up question to that then, you're suggesting that all drugs may potentially cause sedation or drowsiness? Is that my understanding?

DR. SPILKER: Yes.

DR. SOLLER: Thank you.

You know, I think it's important to think about how far we want to tease out some of the laboratory values and how far we're going to look at those laboratory studies.

Dr. Galson, Dr. Ellingstad, do we have anything we need to do now? I'm happy to return to my answer later, if I need to.

DR. ELLINGSTAD: This is Wednesday, and they do test the fire alarms. I'll ask our staff to verify that that's what it is, and we'll --

DR. SOLLER: Okay. We'll see how well we do on divided attention.

DR. ELLINGSTAD: -- deal with it. Thank you.

DR. SOLLER: I think it's important that we think about how far we want to tease out the laboratory values and particularly as we look at simulator or other types of studies, where what we see are perhaps doses that are not those that are necessarily used in an in-use situation.

I'm speaking from an OTC context in certain cases. Our view is that the broad term sedation as has been defined in the clinic and the clinical studies has been appropriately looked at for OTC medications. This is well studied through the OTC review.

There was a great discussion on the issue of drowsiness and the effect on driving as well as operating machinery for certain of the products and even beyond the antihistamines, and when you look at an

RX/OTC switch drug, again a very thorough clinical experience, and I think in the end, when you match that against what we're seeing in the AER profiles as well as the larger epidemiologic studies, I think we're on track in focusing our efforts on the kinds of warnings that would direct people about what products might cause drowsiness or impairment.

DR. GARBER: Then your colleague suggested that all those drugs might cause impairment. Are you in agreement with that?

DR. SOLLER: No, I'm not in agreement with that.

DR. GARBER: Okay. Thank you.

DR. SOLLER: Although I will say, you know, I'm talking about recommended dosages for OTCs in that context.

DR. GARBER: Understood. I'd like to pass the questioning now to Dr. Temple for the FDA.

DR. TEMPLE: Is this on? Yes. A number of you have been talking around this.

Do we have enough information to think that any one of these kinds of tests provides different information? For example, Dr. O'Hanlon has developed one specific test for driving based on lateral

movement. Dr. Weiler has shown a method for assessing a wide variety of functions, and Dr. Kay has talked about a variety of things that tell how alert you are and whether you fall asleep when you lie down during the day.

Are all these -- do we have any way of knowing whether all of these things tell us the same thing or whether they're actually different? Are you just as informed if you know that a person is not alert on one of the standard tests as you are if you have information about lateral motion?

Is there any way to tease this out? Obviously my question goes to whether we should be thinking of a standard battery of tests or whether, as we have sort of concluded in the past, that once you know a drug is sedating, it causes all of these problems, and you just already know that and the rest doesn't add much.

Can any of you comment on that?

DR. KAY: From perspective neuropsychology, I would say that it's important that we study not just one test as an indicator of whether there is sedation because we look at medications. Some medications will affect psychomotor functions, skilled motor activity

and have very little effect, if any, on cognition.

For example, if you look after days of dosing with some of these medications, we cease to see the effects on measures of attention, concentration, vigilance, but we can still detect significant effects in psychomotor ability, especially under divided attention.

So that, I think it's important that we realize that different drugs are going to affect the brain differently. We're talking about central nervous system function and differential effects of different agents depending upon what neurotransmitter systems are being disrupted by that particular medication.

DR. O'HANLON: An investigator uses the tools at his disposal. I don't have an $80 million simulator. On the other hand, I did work in a country that allowed me to test drug effects in a real environment which would be difficult in the United States, but it could be done. As a matter of fact, it started here.

What you have, though, is a consensus across people who devote full time to assessing the behavioral toxicity of drugs regarding some drugs, and there is a gray area where various investigators will argue with

each other about whether this drug belongs in the next category or the next category down, and then we go into a white area where nearly all investigators agree that the drug is relatively safe.

In spite of the diversity of methods, experience with these drugs in performance testing laboratories has led to a very broad and very strong consensus about the worst and the best drugs. I don't think that the diversity of methods is the issue.

Everybody uses what they have to, but the conclusion, the focusing, the narrowing of opinion on certain drugs is inescapable. It was there 15 years or 17 years ago, Bob, when I visited. It's there, and it's better today.

DR. TEMPLE: But that, in some ways, is what I'm getting at. Should we be content if any one of these methods, even if it's -- whether it's an actual driving method or it doesn't involve driving, shows impairment, do we then more or less have our answer, assuming we've got data over time and data related to dose and all that, or do you actually need a driving test?

DR. O'HANLON: Impairment is not a real -- something in itself. I mean, drugs can be impairing.

You can have such a sensitive test that you can measure tiny impairments of minuscule amounts of dose of drugs relative to therapeutic doses. That's not important.

You need an external standard. We've tried to use the blood alcohol concentrations as our external standard of safety. It may or may not be the best. You need that, and if you have that, you can -- impairment is not the issue. It's impairment relative to a drug which is known to be behaviorally toxic and known to kill people at a rate of 40,000 a year in the United States. If you have that, you have a very good screening test.

DR. WEILER: I'd like to make one point. This raises a very -- I think, a very important issue, and that is, that it's very clear why drowsiness has been something that we've been able to quantify and put into package labels, because we can measure it, and it's pretty clear what we're measuring. It doesn't matter whether it's a visual analog scale or collecting adverse events or whatever we're doing. We can measure drowsiness.

We've gotten into a very difficult area when we talk about measuring impairment because there are so many different tests, and there are so many different

standards.

I mentioned that driving is a real world task, but it's not the only real world task. The person who operates heavy machinery, the person who works in a shop and has to operate equipment there, those are also very real world tasks for those people, and the issue's going to come up in developing some kind of a standard, some kind of a way that we can quantify the impairment that people will accept.

I agree that it shouldn't be one test, but there should be a group of tests or a group of standards by which we can determine impairment, and it shouldn't just be drowsiness. We shouldn't just say that the lack of drowsiness is okay, you're fine, or if you're drowsy, that we don't have to go further in quantifying the level of impairment, and that's going to be the difficult task.

I don't think we're going to come up with a single test today. I think that's going to be a task that you folks are going to have to work with and some time come down with a series of tests that will be acceptable, that will work, that will allow investigators to be able to look at the question and know what kind of guidance they need to determine where

they're going to go next in looking at the impairment of these various drugs.

DR. SOLLER: Just a comment, if I could. Thank you, Dr. Temple.

I think you're on target when you restated the question, do we actually need a driving test for every drug, and I don't know. Maybe the investigators would say so, and I do find the results interesting, but from the state of the knowledge that we have now, the questions about extrapolating from laboratory to in use and whether these particular studies are validated and which ones to pick, I think you're probably on target, at least where I thought you were going, in terms once we know that it's sedating, do we have enough at this particular time?

I think if you know a product produces drowsiness, then in some individuals, potentially it will affect performance, and if you find that you have ambiguous findings around that particular effect in a battery of clinical trials that are done on a new chemical entity, then maybe on a flexible case-by-case approach or perhaps that's the way to do it, to look for further performance effects that might be seen to better elucidate what's going on until we have, I

think, more information.

DR. TEMPLE: This isn't a question. It's really a comment on what everybody said, but one of the things that was very striking to me was the pretty precise ability to see how long impairment lasted with some of these tests, which is obviously crucial, Bill.

You know, you can put watch out for drowsiness on your label, but that doesn't tell you about dose. It doesn't tell you about duration. It's really not enough information, given what we've just seen. There are big differences in how long the effect lasts, you know.

Sonata wipes you out for the first four hours and then nothing. That's different from the other drugs. Those seem very important.

DR. SOLLER: Well, I haven't seen that one on the switch list, but if I could comment, it's important to think about, and I'm again talking from an OTC standpoint, not for prescription products, but to think about what does go on the label, and what is transferrable to the consumer, and what they can act on, and at least from looking at the information we have at hand, we're not seeing that signal that would suggest that what has been done by FDA and what is now

being done with the new drug facts label, and I can say that most of the antihistamine products are already in that label and all will be there by May 16th, 2002, the compliance date.

So, we're in the process of a very large change in information that's going to be conveyed to the consumer on what is already apparently a very good AER profile for these products.

DR. SPILKER: I wanted to clarify my response briefly to Dr. Garber's question before.

I was saying that drowsiness or sedation is likely to be reported by at least some patients for all drugs, not that this is considered or the drug is considered as impairing or as clinically significant.

But when you do clinical trials or you collect adverse reactions, you will always find reports that some patients are sedated or drowsy.

DR. GARBER: Thank you for that clarification. If I can follow up just briefly again, as we've heard other people state here, are you suggesting that that subjective report of that adverse event may not be a good indicator of whether the drug is impairing for the purposes that we've been discussing today?

DR. SPILKER: Yes, I would certainly feel that.

DR. GARBER: Okay. Thank you.

DR. TEMPLE: But, I mean, we know that all so-called non-sedating antihistamines have reports of drowsiness, but they're equal to the reports of drowsiness in the placebo group.

So, we conclude they're minimally impairing. You don't mean everybody's going to report drowsiness from time to time? So, you don't mean that has anything to do with the real effect? You wouldn't really know that.

DR. SPILKER: Well, I agree with you. I'm just commenting on the fact that you will see these data, and then we interpret it the way you do.

DR. WEILER: Could I make one more comment? The issue about quantifying the impairment is important or otherwise we'd trivialize the warnings. If we put a warning on every antihistamine that it's impairing, we then send a message that it doesn't matter what you take, and so the really impairing drugs are drugs that people are going to take just as commonly as those that are either minimally or non-impairing at all. So, it is important to quantify the risk in some way, if we

can.

DR. SWEENEY: I have a question for Dr. Weiler. Have you used the driving simulator to test the effects of any specific over-the-counter drugs, and can you describe the results?

DR. WEILER: Well, we have used it in a study that we looked at diphenhydramine, and we compared it to alcohol. I could review some of those data, if you'd like to, very briefly.

DR. SWEENEY: Please.

DR. WEILER: Okay. Do we have our AV person here to --

DR. SWEENEY: Anyone for AV help up front, please.

DR. WEILER: Try to go through this very rapidly. We do have some data on the point. We looked at the Iowa Driving Simulator which was slightly different than the new National Advanced Driving Simulator in that it doesn't have a track. It is a motion base, but it doesn't move on a track.

This was a simulated driving. There were two phases. The first phase was about 30 percent of the drive, and it's following a car. The second phase is going through a variety of curves and driving as a free

agent as you typically would.

Next. We looked at coherence as the primary end point, and on this slide is an example of the worst, the best and the median coherence. Is there a pointer on this thing? The big button. You'll just have to read worst, median and best, and the bottom one is the best. It shows really close following, and it happens to be in somebody who was drunk.

Next slide. And the point is that someone who is drunk can follow very closely, but that's the only test they can perform well, and in this particular case, we found significant differences between fexophenidine and diphenhydramine, alcohol and diphenhydramine, and placebo and diphenhydramine, and in fact, in this particular end point, the diphenhydramine group performed the worst.

This was a divided attention task. They did well. The alcohol group did well at performing this task but nothing else very well, and the alcohol was .1. They were dosed to .1. I'm not moving this thing, am I? Oh, okay.

This is minimum following distance, and it shows significant differences between the fexophenadine and alcohol and placebo and alcohol. Now, we're

starting to see the alcohol group not perform very well.

Steering instability is something we can measure very easily in the facility. We found differences between diphenhydramine and fexophenadine, diphenhydramine and placebo. I won't go through the other groups because I really think the issue here is the impairment that we saw with the diphenhydramine.

Steering instability in the phase where they drove as a free agent, we saw the same kind of results. Again diphenhydramine impaired and caused steering instability. There were left lane excursions and that's important obviously because you won't want to be driving in the lane where oncoming traffic is coming, and this gave us an opportunity to look at that, and again you can see the diphenhydramine group stands out with differences between it and the fexophenadine and differences with the placebo group.

We looked at self-reported drowsiness, and as expected, the diphenhydramine group had the highest percent of self-reported drowsiness, but, and I think this is probably one of the messages that came through very loud and clear, is we've got really nice P values looking at the correlation between drowsiness and

performance impairment.

We've got P values that are fine. Those are in the parentheses, but when you start looking at the R values, which are really more important, the correlation, we get very poor correlation. It's highly significant for a very small percentage of the population. That's really a problem because the people who thought they were drowsy and wouldn't drive, the cues weren't there, and in fact, I don't know how well this projects, but if you look at the very drowsy drivers, they aren't the ones that had the accidents. The accidents are in red, and there's one in black that are -- I'm sorry -- the black is the median.

They're in red, and they demonstrate where the crashes were in a scenario that we set up, and we didn't see crashes necessarily in the most drowsy individuals. We did see crashes in those who had the high crossing counts, so that those people who drove into the left lane were more likely to have a crash in this last event. So, that's a really concerning result.

I'd be happy to show some video clips if you want. I've got a two-minute video. It's up to you, if you want to see it. Yes? Okay. We'll do our best

here. This is certainly multimedia time.

(Video tape shown)

DR. WEILER: We're showing the Iowa Driving Simulator. This is a control room in that old facility. The way we take somebody up to the facility is they walk up the ramp, and you can see the dome structure. This is getting in the car. This is very similar to what NADS is, a regular car, seatbelt, adjusting the mirror. Again, the control room controls the way the car drives, and this is what you would see if you're sitting in the driver's seat.

It doesn't -- it isn't easy for me to see here. I hope you can see where you all are sitting. Again, there's a side mirror rearview. We had 270 degrees of visuals, and you can see the motion. It was very realistic, again very similar to NADS, it just doesn't move on a track.

You'll see four panels, a driver right there. Let's see. You can see steering instability. We can measure that, and we can view it. Here's the center insert that shows the speed. We see where the foot is. Acceleration and braking are recorded and that's a view of the bay itself showing frame counts.

Here, we're looking at the ability of the car

to follow. Individuals who were on placebo were able to follow the car at a comfortable distance. In this case again, a person showing steering stability. She's able to drive real well and follow the car, does a nice job.

I don't know if this is going to demonstrate it, but we were able to measure the distance, and the varying distance was tremendous in the people who were on diphenhydramine. Here, we see an example of alcohol driving over the center lane.

Now, this is the last event where I talked about crashes. It shows the person crashing. These aren't things we'd want to be doing in the real world, and we can measure those. I mean, we can actually measure the fact that that individual ran into that tractor-trailer coming at him, and we were able to look at those.

This study wasn't powered for that, but it does allow us to do that in future studies. We can do either frequent events or we can do infrequent events to measure these kinds of things.

DR. TEMPLE: When he crashed, did he fall asleep briefly? Is that what the assumption is?

DR. WEILER: Yes. In that particular

individual, he was having a lot of problems getting around, and he did hit the oncoming vehicle.

What was supposed to happen was that they had driven this scenario three times previously. It's a 45-to 50-minute drive, and they're pretty well lulled to sleep at the end of the drive. We're at the end of the drive for the fourth time, and so it wasn't powered for this particular event, but we wanted to throw it in and see what would happen if a car pulled out that had been sitting in the driveway every one of the three previous drives, and so it pulled out, and we measured the time, we can measure reaction time, from the time it begins to move until the time it's blocking the lane.

What's supposed to happen is the car blocks the lane, plus there's a vehicle coming in the other lane. You've got some choices here, and the best one is to stop, and the people would stop generally, but some people would go into the far lane.

We had one woman who was so drunk that she was in the far lane to begin with and actually got able to get back to the right lane before the tractor-trailer came. So, we have a variety of different things, but that scenario is set up. It's an identical

scenario for everybody. We can run them through it. We can categorize the events.

It allows us to do some really tremendous things that are very well controlled, like we would like to do in a science laboratory, where we can actually look at events and control for everybody passing through the study. It's wonderful the way we can look at these kind of things in that setting.

DR. TEMPLE: This, I'm sure, is going to seem like a naive question. Are you trying to find out whether people are in a state where they're likely to actually fall asleep and therefore run into something or is their function impaired even if they're not asleep or both?

DR. WEILER: Well, our interest was really looking at the end points that were important and not -- sleepiness and drowsiness, if the person can stay awake and drive well, is fine, and that was my contention on one of the early slides, was that if you're drowsy, but you're driving okay, it's not a pleasant feeling, but that's not really what this is about.

What this is about is the individual who's impaired. Our end points that we're most interested in

are those that reflect impairment, inability to control the car, inability to keep yourself in your lane, keeping the lateral position where it should be. You pick the lane of best fit and stay there, so you're not over-controlling, a lot of steering instability. We don't want that because we know that predicts a bad event, a crash or some bad event occurring.

We looked at drowsiness. We looked at questions of do you feel impaired to predict those kinds of things because we thought that was important. We find a tremendous disconnect, as the literature demonstrates, but our interest was in impairing. What was impairment?

DR. TEMPLE: But Dr. Kay showed data that people had way decreased sleep latency, even if they did not feel impaired. So, whether you're going to fall asleep or might not relate to whether you feel drowsy.

DR. WEILER: That's correct. That's why we feel it's important to cross correlate, and you may say cross validate, these various tests against each other. I believe that's very important, so that we understand the consequences of changes in the mean sleep latency and some of the other tests that would predict

impairment.

But we have a real world task. We can either do it with on-the-road driving, things that we've done, or we can do it in a simulator. Again, we think there's some advantages. In some cases, there are advantages of real world driving in a real car, and in other cases for the simulator, but the point is it's a real world task, to which we can correlate some of those other tests, low fidelity, low in simulators, and some of the other cognitive tests and some of the other tests that were described, allow us to run the continuum from a facility that's really the high end to the studies that are obviously a lot less expensive to perform, but we can cross validate each other against the other tests, so we can look at how they predict the impairment in a real world task, driving.

DR. SOLLER: I'd like to -- can I make a comment just by way of putting that in perspective? Because I think that study was, as I saw it reported out, had dramatic headlines about the comparison of alcohol to the OTC in question, and just by way of perspective, from the prevalence studies, I'm remembering that the fatal traffic accidents related to alcohol were upwards of 50 percent or more, and I think

one of the questions you have to ask is that if it translates out from a simulator study that alcohol is worse than a particular drug, you have to ask where are the crashes, particularly given the very large usage profile for some OTCs in this regard or other drugs.

It's possible that one of three things is happening. The in use antihistamine drowsiness is not happening as much as we think. There's individual variability, 10 to 15 percent, depending upon the dose, the drug, the condition. When it does or if consumers think that it may because they read the label, they can compensate. They might not choose to drive. They might chose to stay home in bed with their particular malady or third, the simulator studies may have some limits in terms of how you extrapolate that out to real world.

The other comment I wanted to make is that just by way of putting this in perspective, often the 50 milligram dose is the one that is chosen in these particular studies, and from the standpoint of usage patterns, only a minority of the number of different antihistamine-containing products recommend only the maximum dose for this type of antihistamine, the 50 milligram dose.

They're usually recommended in the context of a 25 to 50 milligram dose for diphenhydramine, and many products only have the 25. The expert advisory panel and FDA in the final monograph recognized that consumers would choose these products based on labeling and based on their experience.

The so-called PM products or the night-time products have 50 milligrams as the recommended dose but with directions to take at bedtime, and I think this is important as we think about the range of drowsiness, this 10 to 50 percent that we see for this class of drugs, the dose, the underlying condition, the fact that concomitant medications are taken in combination like a sympathomimetic, because there is extensive variability.

So, in sum, I think you need to take into account usage patterns when trying to understand the practical relevance of simulator studies and also recognize that the consumer's being informed that a market, a very significant effect, market drowsiness, may occur with the product, and in a separate part of that warning, being warned to use caution about driving a car or operating machinery.

That, with what has been very extensive

publication -- public education on read the label, I think, can be supportive of what we're seeing in the post-marketing surveillance studies and the other prevalence studies.

DR. KATZ: I have a question about time course of effect. We've seen some information about the time course post-single dose, but what about post-multiple dose or drugs to be given chronically? Is there an accommodation to this effect over time?

DR. O'HANLON: Russell, are you asking me?

DR. KATZ: Anyone who knows.

DR. O'HANLON: Okay. Those figures that I showed were generally the second night of use. We have done some chronic dosing with hypnotics as well as with most other CNS active medication that we've studied.

There generally is the phenomenon of tolerance, as you'd recognize. On the other hand, there is also the phenomenon of accumulation. Dalmane's effects increase for a week as with accumulation and then begin to decline afterwards with developing tolerance.

As another example, using Ativan, two milligram BID, which is a pretty hefty clinical dose, with anxious patients, we found out that the patients

drove very badly the first day indeed and felt very -- sedated is not a good word. They just felt bad. They felt sleepy. They felt ataxical, all kinds of things. By the end of a week, they were still driving bad, but they felt much better.

There was a decline in impairment over the week. There was a greater decline in subjective drowsiness, and the decline was about the same as the accidents and the number of injured, including fatally-injured drivers, in Saskatchewan as a function of time from the initial prescription.

There is a drop in the relative risk, taking Lorazepam, from 13 times normal in a first week all the way down to two times normal at the end of a month. That's the kind of pattern we were seeing. Yes, tolerance does occur. Yes, you are still in danger of a fatal accident at the end of a month in spite of tolerance occurring.

DR. WEILER: I certainly agree that these studies need to be conducted after first dose and at steady state, but one of the things that we ought to recognize is compliance is a terrible issue with drugs that we prescribe, and many of these antihistamines are really taken on a PRN basis.

So, if we actually look at the use of the drugs, we tell somebody to take the drug when they're supposed to take it, and they really don't take it that way, they take it now, and then they don't take it tomorrow or the next day, they take it the day after.

It makes it very difficult to look at impairment. So, I think you can't just look at steady state. You really do have to look at the effects after a first dose or acute intermittent use.

DR. KAY: When we've looked at steady state, what we have found is that you need to think again in terms of these different dimensions of sedation.

With respect to self-report, we have found, for example, with diphenhydramine, that 25 milligram QID dosing, people continued to show significant fatigue with five days of that steady state dosing on self-report measures. So, that would be looking at self-report. A recent study looking at Citerazine, showing significant self-report sedation at seven days of dosing. So, self-report seems to persist.

With respect to the physiological measures, we see tolerance, clearly, in our sleep latency testing that we do. If we continue night-time dosing with Chlorpheniramine for four nights, by the fourth night,

the eight milligram dose was pretty much close to the 10-minute mark. There had been quite a reduction in the day-time sleepiness.

The higher dose, the 12 milligram, was still at about eight-minutes sleep latency, which is clinically abnormal. So, there is evidence physiologically of tolerance.

In terms of the cognitive tests, those seemed to develop some kind of -- I don't want to call it tolerance but more adaptation. You learned to function under the influence, and we began to see the dropping out of the cognitive effects after about three days of continued dosing, even, you know, with several of these medications.

But with respect to psychomotor, that's why we can't just rely on any one measure, we have shown, for example, at the 25 milligram diphenhydramine dose on that tracking test I showed you, 15 percent of the subjects on diphenhydramine crashed on Day 5 compared to zero percent on placebo on that kind of measure.

So, psychomotor performance can persist, and I think John or Jim might be aware of some research done in the Netherlands by the military looking at three weeks of antihistamine dosing and again showing

on their dual tasking test a persistent psychomotor effect, but the self-report effect was dropping down, and the other cognitive effects had disappeared.

DR. ELLINGSTAD: I might interrupt. I think we've reached a point where we probably could use our first break of the conference. I'd ask everyone again to develop their questions and the audience to submit them on the note cards, and the parties to be assembling theirs.

We will reconvene at 10:15.

(Whereupon, a recess was taken.)

DR. ELLINGSTAD: A couple of things before we begin. There's apparently been some confusion about where to get cards. So, I'd ask the staff who have cards to distribute to collect questions to make themselves known and wave your cards around.

DR. GALSON: The card ladies are back there waving the cards.

DR. ELLINGSTAD: So, anybody that needs those, you know, please summon them and turn in your questions. We have at the moment one individual who has indicated that they will be making an audience presentation. That's in your agenda at 11:15.

Anybody else that falls into that category,

please check at the desk outside, and we would need to have them registered immediately before that would happen.

Okay. We will resume, and before I turn it back to the Technical Panel, let me exercise the prerogative of the chair and sneak in a question here.

It was interesting, the discussion, I guess, that started with Dr. O'Hanlon, that referred indices of impairment to alcohol, and what I'd like to ask as sort of a general discussion of that as a calibration standard for impairment, you know, from other kinds of agents, and my assumption is that you're going on the basis of a long history of epidemiological research that associates various levels of blood alcohol with known probabilities of accident involvement, etc., and then makes the logical extension that from that, we can use that as a calibrating standard for impairment and other drugs.

Would you comment, if I've mischaracterized that logic?

DR. O'HANLON: Thank you, Mr. Chairman. I'm glad to have this opportunity to expand a little bit on my five-minute presentation.

I used alcohol as a standard in two ways.

When I compared the epidemiological data, the limited epidemiological data concerning three hypnotics, I was comparing it to the Borgenstein, the famous Borgenstein epidemiological relationship between blood alcohol concentration and the risk of an injurious or actually in this case fatal accident.

When I was referring to the empirical data from our tests in the Netherlands, I was making the comparison to data we had collected in a special calibration study. Alcohol was probably the most dangerous drug we ever studied, and we did not do that particular investigation on the real road in traffic as we did subsequently with every medicinal drug.

Rather, with the help of the Dutch Province of Ronaken and the traffic enforcement, the law enforcement personnel, we closed a 15-mile segment of secondary highway, and we took a group of 24 social drinkers defined by sociologists and psychiatrists as representative of social drinkers. As close we could come to a really representative group were civil servants, and we had 24 civil servants who undertook the test sober and at .03 blood alcohol concentration, .06, .09, 1.12, and we were very pleased to see that our primary outcome variable standard deviation of

lateral position increased exponentially with the blood alcohol concentration.

The correlation between mean concentration and mean SDLP change was .99. On the basis of that strong relationship, we developed an alcohol calibration curve which allowed us ever thereafter to state the amount of weaving and swerving that occurred after medicinal drugs relative to the equivalent blood alcohol concentration.

I think that could be done for every test and should be done. Now, alcohol is a most complex pharmacological entity. It is not the same as any other drug. So, this comparison is limited but nonetheless, it's the best we've got with the most notorious hazard to traffic safety, pharmacological hazard being alcohol.

DR. ELLINGSTAD: Okay. Thank you.

Dr. Soller?

DR. SOLLER: Just a comment, and I know we're going to be talking about the labeling tomorrow. I would ask that you perhaps bear with me because as we think about these kinds of standardizations, ultimately they potentially can have a public health intervention impact in terms of where you go, and that's where I'm

coming from in this particular comment.

I think from the standpoint of looking at these kinds of relationships, and I'm not going to argue it from a scientific standpoint but that stamp, they imply sort of an all or none standard, and I think that's important in trying to think about what that might look like ultimately, and that may be appropriate from a scientific standpoint, where you're investigating these products and trying to look at comparisons in the scientific framework in a laboratory of clinical setting and that kind of framework, looking for those kinds of comparisons.

But I think from a labeling standpoint, it's totally inappropriate, and the reason I say that is that for at least the products that we are concerned with in the OTC market, there appears to be a considerable amount of individual variability, that these are effects that may occur, not necessarily occur all the time in all people, and two things can ultimately happen, and that is, for those individuals who have a pejorative view about alcohol, having something like that translated into labeling would unfairly disparage the product, and for those who are interested in abusing products might well lead them to

think that they're going to get alcohol-like effects.

So, just a comment as we think about how these things might ultimately translate out.

DR. ELLINGSTAD: Okay. Thank you, and we will discuss labeling and get into the actual interpretations of --

DR. SOLLER: I understand.

DR. ELLINGSTAD: -- that later. The point of my questions to Dr. O'Hanlon was principally from a psychometric point of view, of having a reference against which -- that has been reasonably well accepted and, we presume, reasonably well empirically established as an impairing substance.

DR. KAY: Just briefly, Dr. Ellingstad. Also, blood alcohol equivalents have also been worked out for many of the cognitive and psychomotor tests.

DR. ELLINGSTAD: Okay. Thank you.

DR. KAY: Expressing the amount of impairment in something like an alcohol-type thing.

DR. ELLINGSTAD: Thank you.

Let me turn it back to the Technical Panel.

DR. GARBER: Just before we get into our last few questions, I did have a couple of comments from the audience during the break that suggested that while

those of us here on the Technical Panel and the Witness Panel are certainly well aware of all of the various names by which the medications are described, some of the folks in the audience are not as well versed in pharmacology.

If there is no objection to this on the industry's behalf, I would like to ask if we can at least -- and recognizing that the trade names of these drugs are not the only names by which they are marketed, but if we can perhaps indicate what some of the common trade names may be for these medications, just so that our audience understands what we're talking about when we are discussing some of these drugs.

Is there any objection to that on --

DR. SOLLER: I thought we were here to talk about the ingredients. Very purposely, we did not include the trade names in the AER analysis that we presented because of the issues of causality and mentioning one trade name and not mentioning all, that's a certain degree of unfairness as well.

I would opt for dealing with the ingredient names.

DR. GARBER: Okay. Then I'll have to ask

that if we can at least describe what the drugs are commonly used for, unless there is an objection to that on behalf of the industry.

DR. SOLLER: Oh, I think that's fine. In fact, I mentioned for antihistamines, they are used in cough/cold preparations, for runny nose, sneezing, for cough. They're used -- some of them are used as sleep aids. Some are used as anti-nausea medications and others for -- and all of them for allergy symptoms, by way of examples.

DR. GARBER: Okay. And I'd like to -- if we can, when we do discuss a drug or if it's something that we haven't mentioned in awhile, if we can make that same -- if the presenter can make that same comment, just to note what we're talking about for those of us who are not all that familiar with the medications and their uses.

Thank you. We have, I think, one or two more questions from the rest of the Technical Panel.

DR. TEMPLE: Much of the data on impairment was presented as changing meanings. Do any of these studies allow one to determine whether what you're seeing is a fairly consistent change in the entire group or a particular subset of a population that is

driving?

In other words, how much individual data do you have versus group data?

DR. KAY: With the cognitive testing, obviously we're able to test larger groups than we do in a driving situation. In fact, typically when we have a hundred subjects, a third receiving a positive control, the third receiving an agent under study, and a third receiving placebo. We're trying to find out whether there's any difference between the drug under study and placebo, and to demonstrate that we have sensitivity to sedation, we include a positive control, and with the size of the groups, we typically can look at specific groups.

For example, when studying diphenhydramine, this one we've been talking about, the cold, allergy and sleep medication, that we basically find that only a third report feeling sleepy. Actually, that was a recommendation by the FDA. Look and see what percentage of the people in your study are reporting sleepiness. We did.

Then we looked specifically at the two-thirds that didn't feel sleepy, and we found that those individuals were just as impaired on the cognitive

measures as people who felt sleepy, you know, that lacked awareness.

So, yes, we could break it down. We have a large enough group. We can find out within a group what's going on.

DR. TEMPLE: But it's not just the little subset that's driving the mean; it's --

DR. KAY: No.

DR. TEMPLE: -- more than that?

DR. KAY: We analyze a study not just looking at mean but also non-parametrically in terms of the percentage of people showing an impairment. For example, on the psychomotor test I mentioned on Day 5 of dosing, 15 percent crashing would be abnormal versus zero percent on placebo.

DR. WEILER: Another issue would be to look at, as we do with the effectiveness responder, looking at an analysis of responders. We could be looking in this case at an analysis of those who have the adverse event.

The other thing that's really important to mention again is that the control groups that we use, if they're healthy people, are going to be different than if we use people who have allergic rhinitis, for

example, in season, and it may be important to do the study in season rather than out of season.

So, we may justify giving them the drug out of season, and it may not be the same thing as coming in and driving when they're sick, they have a runny nose, itching and all the symptoms and feel drowsy to begin with.

So, a lot of variables, not just the dose levels, not just the reaching steady state, but the characteristics of those subjects in the study group would be very important when we're looking at impairment.

DR. O'HANLON: Our studies were typically done with 20 to 30 individuals, being patients or volunteers. That's too few, we agree.

As far as making an extrapolation of the population, we have two ways of doing that. First, at least in the healthy volunteers, we'd give twice the recommended dose. If nobody has responded or very few to the recommended dose, and they still don't respond to twice, we can be pretty sure of the safety of that particular drug.

Regarding are we looking at a few outliers that inflate the mean, in the case of seriously-

impairing drugs, which antihistamines, by the way, are not in our view, then the drugs which cause more change in driving performance than the blood alcohol concentration .10 affect virtually everybody. That means 19 out of 20, 28 out of 30. If the effect is that strong, we are very confident that it is a consistent effect across our subject sample.

DR. KATZ: I had a question for Dr. Kay. You had said that your results on your -- if I heard you correctly, your results on your cog screen testing were predictive of real world situations.

I'm wondering which real world situations and which subsections of the -- or which specific tests or measurement functions were correlated with what those real world situations are, and that sort of raises the larger question, which is, what do we know on the basis of evidence about how these various test methodologies predict bad outcomes? Let's say traffic accidents.

For example, what's the -- Dr. O'Hanlon talked a little bit about the evidence for the lateral sway, but what about the various following closely as a parameter? That's, you know, the various sorts of things that people are looking at. What do we really know about how they correlate with what we really care

about?

DR. KAY: Well, cog screen was a test that was developed for the Federal Aviation Administration as a measure to detect changes in brain functioning which left undetected could interfere with operational performance of an aircraft. It was based on a task analysis of the mental abilities required to fly an airplane, the cognitive, perceptual and psychomotor requirements.

It was later determined that it does predict performance of pilots. In a study done by a major carrier, it was shown that measuring operational performance of the person flying the plane, the commercial airplane, that cog screen was the better predictor than some simulator performance, whether or not the pilot had flown in the Air Force, his knowledge-based test, his IQ test, personality test. So, it's a major selection tool.

It's also shown in studies where -- you couldn't do this in the U.S. but overseas, when we get the flight data recorder and measure landing performance, it was a good predictor of landing performance, and in studies where we have looked at pilots who've been referred for aviation performance